Ductal carcinoma in situ and invasive breast cancer: diagnostic accuracy and prognosis

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Chapter 1

Scope of the thesis

General introduction

In general, diagnostic tests and medical assessments are fundamental for adequate health care management. This also holds true for ductal carcinoma in situ (DCIS), a non-obligate precursor of invasive breast cancer (IBC) and IBC itself. All tests might serve multiple purposes: first, to exclude or confirm whether a suspect breast lesion is present in both the setting of population-based breast cancer screening or at request. Second, if a lesion is confirmed, to classify the lesion and predict prognosis and benefit of treatment. Third, to monitor progress of the disease or to evaluate response to treatment. All these tests lead to detailed information about the subtype of DCIS or IBC, disease stage, risks of progression, and prediction of treatment effect. Obviously, all tests come with intrinsic limitations due to imperfect sensitivity, specificity and accuracy, which also depend on the context of the applied test[1]. For example, certain diagnostic tests can be highly accurate, e.g. detection of calcifications on mammography or recognizing a full blown (pre-)malignant abnormality in a breast biopsy, but the presence of such lesions does not imply lethal disease per se. Diagnosing such lesions that will never lead to symptoms or death is called overdiagnosis[2]. Strictly, the determined diagnosis is accurate, but treating these lesions is defined as overtreatment and will cause unnecessary harm to the patient. Therefore, knowledge about the follow-up of patients diagnosed with a DCIS or IBC is essential to understand the impact of the disease on individual patients as well as on society level in context of the 'benefit-to-harm' ratio. As such, epidemiological knowledge involving analyses about incidence, prevalence and outcome is interconnected with the interpretation of individual patients' test results.

Aim of this thesis

In this thesis, we evaluate the accuracy of diagnostic testing in context of the risk of progression of DCIS and IBC. This will ultimately help to optimize identification and classification of DCIS and IBC, to the disease course, including response to treatment, and to predict outcome.

Thesis Outline

Ductal carcinoma in situ: diagnostic accuracy and prognosis

Part one focuses on classification and associated risk of progression of ductal carcinoma in situ (DCIS). DCIS is proliferation of neoplastic epithelial cells confined to the ductal system of the breast. The incidence of DCIS has increased substantially since the introduction of population-based breast cancer screening while the breast cancer specific mortality is not decreased[3,4]. The majority of the DCIS diagnoses are identified by calcifications on mammograms acquired within the framework of population-based screening programs. Interestingly, only a minority of DCIS lesions

causes symptoms, for example a palpable lump in the breast or nipple discharge. We believe that most DCIS lesions will never progress to invasive breast cancer based on two major findings: i) since introduction of the screening the incidence of advanced stage breast cancer has not decreased[4,5] indicating that we mostly detect indolent breast lesions by screening instead of the lethal ones and ii) autopsy studies found a high incidence of DCIS indicating a DCIS reservoir in older women exists without clinical consequences[6]. At time of diagnosis it is unknown which DCIS lesions will progress to IBC, therefore all patients receive the same treatment as in the case of breast cancer leading to overdiagnosis and overtreatment for the patients with indolent DCIS, i.e. for those lesions that would never progress even if left untreated.

Chapter two *"Ductal Carcinoma in situ: to treat or not to treat that is the question"* provides an overview of the current knowledge of DCIS including how our initiative, PREvent ductal Carcinoma In Situ Invasive Overtreatment Now (PRECISION), manages to discriminate indolent from hazardous DCIS.

To guide treatment decisions, DCIS is classified diagnostically into well, intermediate or poorly differentiated DCIS. Since it is assumed that grade corresponds to prognosis[7–9] in terms of risk of a subsequent ipsilateral DCIS or IBC, this is used as a prognostic test. Multiple guidelines to classify DCIS exist and the interpretation of the same lesion shows variation between observers, resulting in substantial variability in DCIS grading. The study described in **chapter three** shows an evaluation of the differences in histological assessment of DCIS among pathologists around the world. In addition, we explored possibilities to decrease the interpretation differences.

Prediction of outcome in terms of risk of progression is dependent on the type of treatment of the primary DCIS. DCIS is nowadays often treated with breast conserving surgery supplemented with radiotherapy. The added benefit of radiotherapy has been studied in several clinical trials and has been estimated to be 15% absolute risk reduction for any ipsilateral breast event at ten years of follow-up[10]. In **chapter four**, we studied the association of initial DCIS treatment with long-term risk of subsequent ipsilateral in situ and invasive disease to evaluate the impact of treatment strategy in a non-randomized nationwide cohort. Ideally, we would develop a test, for example including age, tumor size and tumor grade, to select low risk patients to de-escalate (radio)therapy. This chapter provides insights in the long-term risks of treated DCIS on population level.

Invasive breast cancer: diagnostic accuracy and prognosis

Part two aims to explore how to optimize the accuracy of clinical tests in IBC patients treated with neoadjuvant systemic therapy. In addition to local surgery, systemic therapies are applied in breast cancer to eliminate metastasis undetected

at time of diagnosis. To determine who will benefit from systemic therapy, risk profiling is performed. Patient characteristics such as age, menopausal status and performance status, and tumor characteristics as hormonal status and HER2 status, tumor grade and size and lymph node status play a role in determining the risk profile [11,12]. These 'classic' characteristics capture only certain aspects of the tumor biology[11,13]. Molecular tests like the mammaprint[14] and Oncotype DX were developed to improve risk profiling. Based on genomic characteristics these assays try to classify patients in high and low risk breast cancer groups. In the MINDACT trial it was found that chemotherapy could be avoided in patients with clinical high, but a genomic low risk[11]. Hence, these assays are increasingly used in research and clinical setting. Before such a molecular test is performed, quality control (QC) measurements such as minimum tumor cell percentage and RNA quality are required. These inclusion criteria result in a selection of a specific group of breast cancer tissue samples. In **chapter five** we investigated if QC variables for gene expression analysis, could lead to a bias in sample selection.

Neoadjuvant systemic treatment (NST) – systemic treatment delivered prior to definitive breast surgery - could be applied whenever systemic therapy after surgery would be necessary according to the Dutch breast cancer guidelines[15]. NST is increasingly applied, because it intends to shrink the tumor permitting less extensive breast surgery and provides information regarding response during and quickly after treatment. NST compared to adjuvant systemic therapy has equivalent breast cancer recurrence and breast cancer mortality rates[16]. After surgery, the response of NST is evaluated in the resection specimen by the pathologist examining the vital tumor cell percentage. If all tumor cells disappear, a pathological complete response (pCR) is achieved corresponding to the best achievable prognosis at that timepoint[17]. Recently, the US Food and Drug administration mechanism for approval of newly systemic treatments is based on improved pCR figures[18,19]. Evaluation of residual tumor cells in these resection specimens is not standardized yet and various classification systems are used. In **chapter six** we evaluated different pathological classification systems: residual cancer burden (RCB), neoadjuvant response index (NRI) and Neo-Bioscore, and established the long-term prognosis based on various categories of residual disease.

Chapter seven summarizes how the results of the studies described above contribute to improve accuracy and clinical utility of diagnostic tests for breast cancer patients. Furthermore, future perspectives are discussed.

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